Direct Interaction of RNA Polymerase II and Mediator Required for Transcription in Vivo

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and well-being even long after their delivery (*7*, *20*, *25*, *31*, *34*).

Importantly, the effectiveness of social-psychological interventions depends on factors in the context. Such interventions are unlikely to be effective in contexts without opportunities for learning. Also, because the present intervention works by changing people's subjective interpretation of ambiguous events, it may be ineffective in openly hostile environments. Lastly, whether this intervention would work among younger or less-select students, or students from other marginalized groups, is an important question for future research (*20*, *31*, *34*). These qualifications noted, the results underscore the importance of social belonging and subjective construal in contributing to social inequality and show how this insight can inform our collective efforts to promote equality in performance, health, and well-being.

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Supporting Online Material

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Direct Interaction of RNA Polymerase II and Mediator Required for Transcription in Vivo

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Gene transcription is highly regulated. Altered transcription can lead to cancer or developmental diseases. Mediator, a multisubunit complex conserved among eukaryotes, is generally required for RNA polymerase II (Pol II) transcription. An interaction between the two complexes is known, but its molecular nature and physiological role are unclear. We identify a direct physical interaction between the Rpb3 Pol II subunit of *Saccharomyces cerevisiae* and the essential Mediator subunit, Med17. Furthermore, we demonstrate a functional element in the Mediator–Pol II interface that is important for genome-wide Pol II recruitment in vivo. Our findings suggest that a direct interaction between Mediator and Pol II is generally required for transcription of class II genes in eukaryotes.

Mediator is a large multisubunit complex conserved in all eukaryotes (*1*). It acts as a link between specific protein regulators and the RNA polymerase II (Pol II) transcription machinery (*2*). Mediator is required at most Pol II–transcribed gene promoters for regulated gene expression (*3*–*5*). In *Saccharomyces cerevisiae*, Mediator is composed of 25 subunits and is organized in four structural modules: the tail, middle, head, and Cdk8 modules (*6*). A direct Mediator–Pol II interaction is indicated by previous copurification, coimmunoprecipitation (CoIP) experiments (*7*–*9*) and by in vivo formaldehyde cross-linking (*10*). A model of the Mediator–Pol II complex determined by electron microscopy (EM) at 35 Å resolution suggests that several Pol II subunits (Rpb1, 2, 3, 6, and 11) might contact the middle or the head of Mediator (*11*). It was recently suggested that Rpb4 and Rpb7 could also be implicated in interactions with Mediator (*12*–*14*). However, the requirement of a direct interaction between Mediator and Pol II for transcription activation has not been demonstrated. Moreover, the identity of the Mediator subunits contacting Pol II is unknown because of the low resolution of the Mediator structure. As a consequence, the mechanism by which Mediator recruits Pol II is poorly understood.

To identify the subunit(s) of Mediator that directly contact Pol II and determine the role of these interactions in transcription regulation, we used an in vivo photo–cross-linking approach based on the incorporation by the cell-translation system of photo-activable analogs of methionine and leucine in proteins [see supporting online material (SOM) text and figs. S1 and S2] (*15*, *16*).

Because EM results (*11*) suggested potential interactions of 16 Mediator subunits belonging to the head (Med6, 8, 11, 17, 18, 19, 20, 22) and middle (Med1, 4, 5, 7, 9, 10, 21, 31) modules with Rpb1, 2, 3, 6, or 11 Pol II subunits, we immunoprecipitated hemagglutinin (HA)–tagged proteins after in vivo cross-linking. Among the 80 pairwise contacts that we tested, only Myc-tagged Rpb3 and HA-tagged Med17 cross-linked (Fig. 1). These results demonstrate that the Rpb3 Pol II

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subunit directly interacts with the essential Med17 subunit of the Mediator head module, in line with the peripheral location of Rpb3 in the Pol II structure (*17*, *18*) and with the general requirement for Med17 in transcription (*4*).

A thermosensitive *rpb3-2* mutant defective in activator-dependent transcription in vitro and in vivo was described previously by Tan *et al*. (*19*). The mutation contains two amino acid substitutions [Cys^{92}→Arg^{92} (C92R) and Ala^{159} → Gly^{159} (A159G)] (*20*) that have a strong synergistic effect on the thermosensitive phenotype. We mapped the mutated amino acid residues of *rpb3-2* on the crystallographic structure of Pol II. C92 is located on the subunit surface, and A159 is close (~7 Å) to C92 (Fig. 2A). We tested whether the Med17-Rpb3 contact is modified in the *rpb3-2* mutant. The in vivo photo–cross-linking approach could not be used in the *rpb3-2* mutant, because the incorporation of the photo–amino acids was strongly diminished due to the mutant slow growth. We turned to a formaldehyde cross-linking strategy and detected Rpb3-Med17 cross-linking in the wild-type (WT) strain (Fig. 2B). This contact was strongly reduced in the *rpb3-2* mutant. CoIP experiments with chromatin and soluble extracts further confirmed that Mediator–Pol II association was impaired in the *rpb3-2* mutant (see SOM text and figs. S3 and S4).

Previous results have shown that the mRNA level of the *GAL1*-inducible gene was decreased in the *rpb3-2* mutant (*19*). We therefore examined Pol II and Mediator occupancy on the *GAL1* gene by chromatin immunoprecipitation (ChIP) experiments after galactose induction. Pol II occupancy of the *GAL1* gene was significantly reduced in the *rpb3-2* mutant compared with the wild type (Fig. 2C). In contrast, Mediator occupancy of the *GAL1* promoter in the *rpb3-2* mutant was similar to the WT level with only a marginal reduction after a 45-min induction. As for the *GAL1* gene, a clear decrease of Pol II occupancy can be observed in the *rpb3-2* mutant, but not for Mediator association to the *ADH1* and *PYK1* genes that are constitutively expressed (fig. S5). Our results suggest that the *rpb3-2* mutant is affected in the Mediator–Pol II interaction leading to defective Pol II recruitment, even though other factors could also contribute to this defect. To investigate whether the decrease of Pol II occupancy in the *rpb3-2* mutant affects transcription in general, we analyzed the genome-wide Pol II occupancy by ChIP followed by DNA hybridization on microarrays. Regression analysis of Pol II binding in the WT versus *rpb3-2* mutant revealed a global 1.5-fold decrease in the mutant with a high correlation coefficient (Fig. 2D), suggesting that Med17-Rpb3 interaction is required for the recruitment of Pol II on most active genes.

To investigate the in vivo role of Med17 in Pol II recruitment, we selected 29 *med17* thermosensitive mutants and showed that 5 of them (*med17-68*, *-158*, *-208*, *-257*, and *-327*) were colethal with the *rpb3-2* mutation (Fig. 3A and fig. S6A). In a *RPB3* WT background, these five *med17* mutants had diverse slow-growth phenotypes at 30°C (fig. S6B). The allele-specific lethality between the *rpb3-2* and *med17* mutations is consistent with a physiological role for the Med17-Rpb3 interaction.

To analyze the molecular nature of the *med17* thermosensitive mutations showing specific synthetic phenotypes in *rpb3-2* background, we determined the Pol II and the Mediator occupancy in the *med17-68*, *-208,* and *-257* mutants by ChIP experiments in a *RPB3* WT background. A strong decrease in Pol II association with the *ADH1* and *PYK1* genes was observed in these mutants compared with the wild type (Fig. 3B). In contrast, the Mediator association (measured by the Med5 middle, Med8 head, or Med15 tail subunit ChIP) to the *ADH1* and *PYK1* gene promoters was similar to the WT level (fig. S6, C, D, and E). The integrity of Mediator in *med17* mutants has been verified by CoIP experiments (fig. S7).

Using random mutagenesis of *MED17*, we looked for *med17* mutants that would suppress the growth defects of *rpb3-2 (C92R A159G)* at 37°C. No suppressor was obtained, but we isolated several *med17* mutants that suppressed the mild thermosensitive defect of *rpb3-A159G* single mutant (Fig. 4A). One representative suppressor mutant, *med17-sup1 (I128V R582G N595D)*, was chosen for further analysis. We determined the effect of *med17-sup1* mutation on Pol II and Mediator occupancy in the *rpb3-A159G* background. Figure 4B and fig. S8 show that the association of Pol II to the *ADH1*, *PYK1*, and *PHO84* genes is slightly but significantly decreased in the *rpb3-A159G* mutant and is restored to WT levels in the *rpb3-A159G med17-sup1* strain. The Mediator association to the *ADH1*, *PYK1*, and *PHO84* promoters remained at WT levels (fig. S8B). As for Pol II, the association of the general transcription factor TFIIH was also diminished in the *rpb3-A159G* mutant, and the *med17* suppressor restored near WT TFIIH occupancy (fig. S8C).

MED17 was initially isolated as *SRB4*, in reference to mutations that suppressed the growth phenotype of truncations of the Pol II Rpb1 C-terminal repeat domain (CTD) (*9*). The *med17* suppressors were unable to compensate the conditional-growth phenotypes of the *rpb1-Δ104* CTD-truncation mutant (fig. S9), indicating that the suppression is specific for *rpb3-A159G*.

A functional link between Mediator and Pol II CTD was proposed after the identification of suppressors of CTD-truncation mutants affecting the Mediator subunits (*9*, *21*), because Mediator plays a stimulatory role in CTD phosphorylation by TFIIH (*7*, *22*) and binds to glutathione *S*-transferase–CTD (*23*). However, a low-resolution model of the Mediator–Pol II complex suggests that, beyond its presumed interaction with CTD,

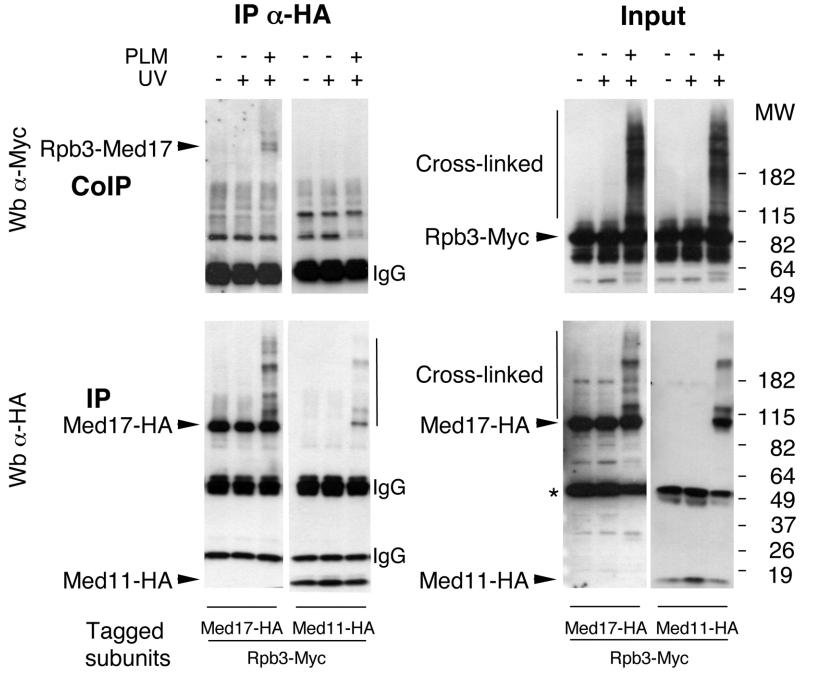

Fig. 1. Direct in vivo interaction of the Rpb3 Pol II subunit with the Med17 Mediator subunit. Rpb3-Myc Med17-HA or Rpb3-Myc Med11-HA strains grown in the presence or absence of photo-leucine plus photo-methionine (PLM) were ultraviolet (UV)–irradiated or not, as indicated. Proteins were immunoprecipitated (IP) with α-HA antibody from crude extracts (Input). Immunoprecipitated or coimmunoprecipitated (CoIP) proteins were analyzed by Western blotting (Wb) with α-HA or α-Myc antibodies, respectively. The cross-linked Rpb3-Med17 band is indicated. The position of unidentified cross-linked proteins with the tagged Mediator or Rpb3 subunits is indicated by a vertical bar. The position of the proteins and immunoglobulin G (IgG) heavy or light chains is indicated. An asterisk marks a nonspecific band. MW, molecular weight in kilodaltons.

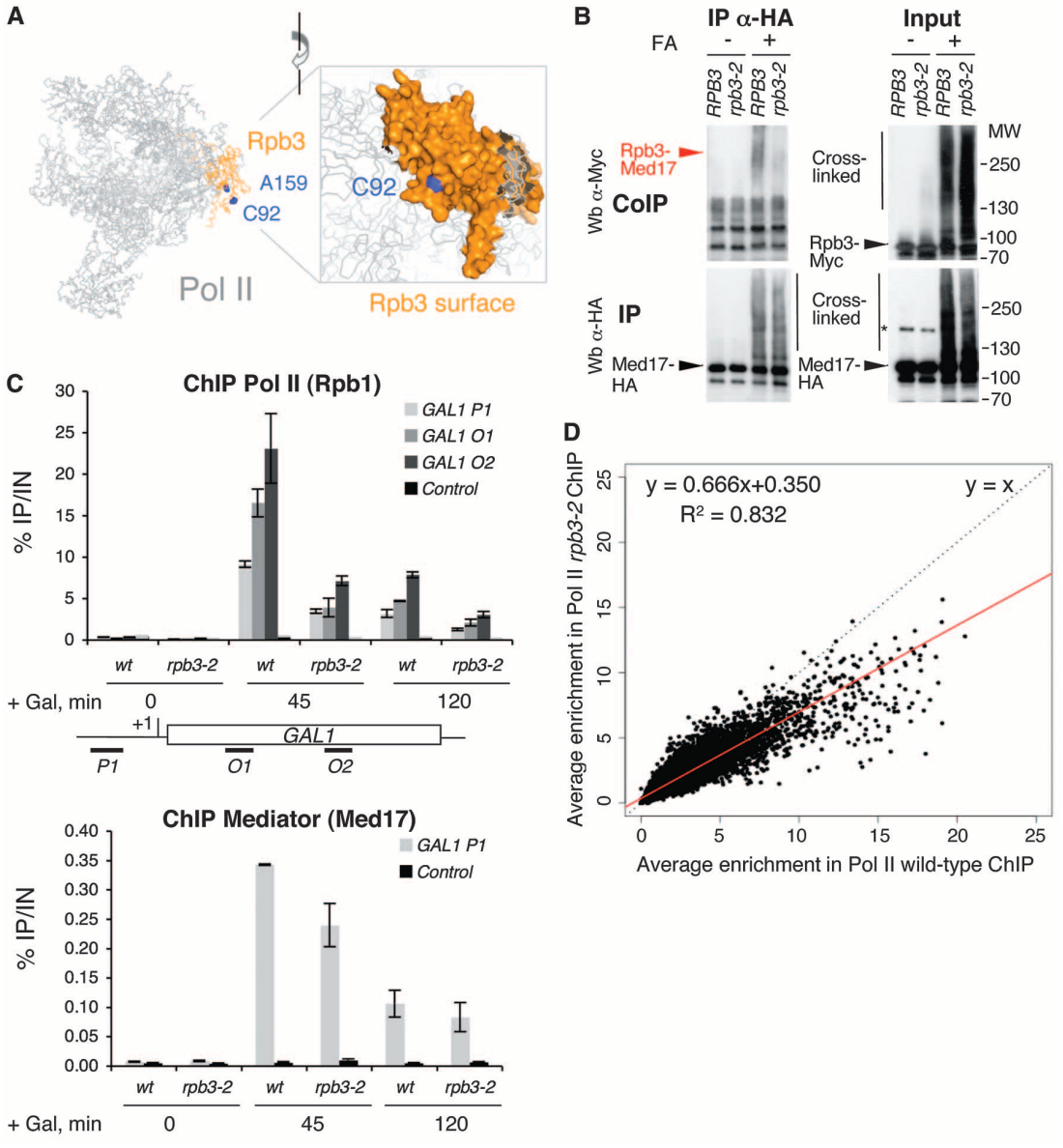

Fig. 2. The *rpb3-2* mutant is defective in Mediator-Pol II association and Pol II occupancy. (**A**) Positions of the residues (A159, C92) mutated in *rpb3-2*. A ribbon model of the yeast Pol II structure (Protein Data Bank code 1WCM) is presented. Pol II subunits are shown in gray, except for Rpb3, which is shown in orange. The blue spheres mark A159 and C92. A box zooms in on the surface of Rpb3 with C92 in blue. A159 is located beneath the subunit surface and is thus invisible on the enlargement. To focus on the Rpb3 surface, the structure in the box was rotated. (**B**) Med17-Rpb3 contact is affected in the *rpb3-2* mutant. Rpb3-Myc Med17-HA or rpb3-2-Myc Med17-HA strains were cross-linked (or not) with formaldehyde (FA), as indicated. Med17-HA was immunoprecipitated with α-HA antibody from crude extracts (Input) and analyzed by Western blotting with α-Myc antibody (CoIP) against Rpb3. The cross-linked Rpb3-Med17 band is indicated in red. The position of unidentified cross-linked proteins with the tagged Med17 or Rpb3 subunits is indicated by a vertical bar. An asterisk marks a nonspecific band. (**C**) Pol II and Mediator occupancy on the *GAL1* gene upon galactose induction. The *rpb3-2* and WT strains were grown in a raffinose-supplemented medium, then galactose was added for 45 or 120 min. ChIP was performed with a α-Rpb1 antibody (Pol II) and with a α-HA antibody against Med17-HA (Mediator). Mean values and SDs (indicated by error bars) of three independent experiments are shown. The location of the polymerase chain reaction (PCR) fragments is indicated (P1, O1, O2). A control corresponds to a nontranscribed region on chromosome V. IP/IN, ratio of immunoprecipitated DNA (IP) over input DNA (IN). (**D**) Genome-wide Pol II enrichment in *rpb3-2* was compared with that of the wild type. A linear regression (red line) and its equation are indicated. The dotted line corresponds to $y = x$. Four biological replicates were performed for each experiment. R^2, correlation coefficient.

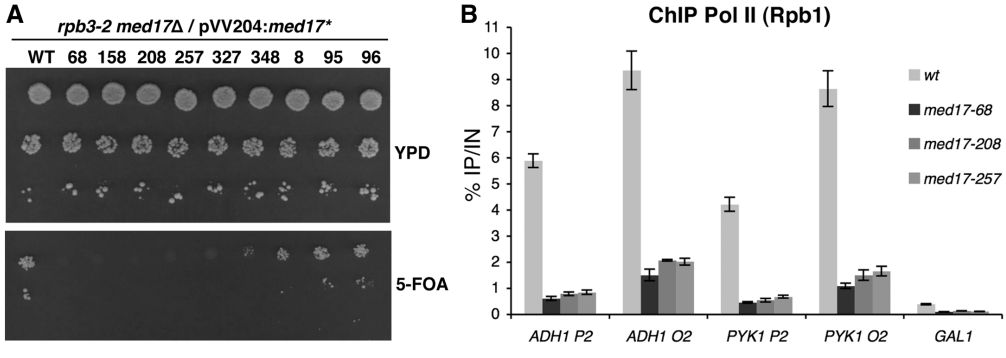

Fig. 3. Specific *med17* thermosensitive mutations are colethal with *rpb3-2* and show severe Pol II occupancy defects. (**A**) *med17* thermosensitive mutations are colethal with *rpb3-2*. Cells were serially diluted, spotted on yeast extract, peptone, and dextrose (YPD)– or 5-FOA–containing agar plates (to counterselect the WT *MED17*-bearing plasmid), and incubated at 30°C for 7 days. (**B**) Cells were grown at 30°C. ChIP was performed with a α-Rpb1 antibody for Pol II. Mean values and SDs (error bars) of three independent experiments are shown. The *GAL1* open reading frame (ORF) was used as a control.

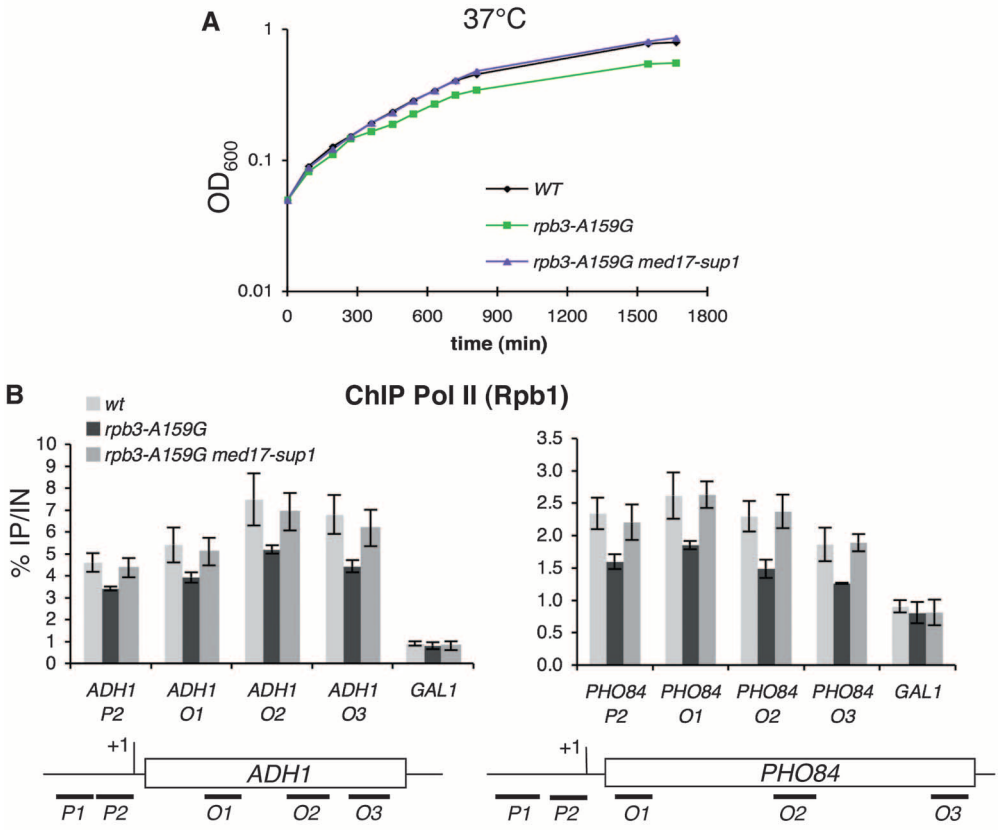

Fig. 4. The *med17* mutation suppresses the *rpb3-A159G* growth phenotype and Pol II–association defects. (**A**) The *med17-sup1* mutation suppresses the *rpb3-A159G* growth phenotype. Cells were grown in a liquid YPD medium at 30°C and then shifted to 37°C at time 0 min. The optical density at 600 nm (OD_{600}) is indicated on the *y* axis. The growth curves for WT strain, *rpb3-A159G*, and *rpb3-A159G med17-sup1* mutants are shown in black, green, and blue, respectively. (**B**) Cells were grown at 30°C and then shifted to 37°C for 5 hours. ChIP was performed with a α-Rpb1 antibody for Pol II. Mean values and SDs (error bars) of three independent experiments are shown. The *GAL1* ORF was used as a control. The location of the PCR fragments is indicated (P1, P2, O1, O2, O3).

Mediator might engage in multiple contacts with the enzyme (*11*). Here, we have shown that Med17 interacts with Rpb3, and we selected *med17* suppressors specific for *rpb3-A159G* that had no *SRB* phenotype. Further, we observed allele-specific lethality between *rpb3-2* and *med17* thermosensitive mutations. The cross-linking approach that we used probably revealed only a subset of in vivo interactions. Indeed, we did not test all potential contacts between subunits of Mediator and Pol II, and we used only two photo-activable amino acids. Thus, it is possible that other contacts exist between the Mediator complex and Pol II.

We showed that the Rpb3 subunit plays an essential role in Pol II recruitment to most class II genes and that the Med17 Mediator subunit function is central to preinitiation complex formation. A direct contact between Med17 and Rpb3 that is structurally homologous to the bacterial α subunit implicated in transcription activation (*19*, *24*) further supports the apparent conservation of the RNA polymerase surface involved in transcription regulation from prokaryotes to eukaryotes, even though the molecular mechanisms and interacting partners differ.

Our results support the notion that the direct interaction of the Rpb3 Pol II subunit with the Med17 Mediator subunit is essential for global Pol II recruitment in vivo. Therefore, Mediator might be considered a general transcription factor (*25*). In addition, with the conservation of Pol II (*26*) and Mediator (*1*), the mechanism of transcription activation by Pol II recruitment through the contact between Rpb3 and Med17 may extend to all eukaryotes.

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Supporting Online Material

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